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Comment

Interpretation of conventional survival analysis and competing-risk analysis: an example of hypertension and prostate cancer

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Most clinical studies use conventional methods for survival analysis and calculate the risk of the event of interest; however, it is important to understand that the study population is also at risk of competing events, e.g. death from other causes. Moreover, the risk of competing events may be dependent on the participants' characteristics. Whether competing risks are taken into account or not, is of major importance when interpreting study results.

Here, we use a practical example to elucidate the interpretational differences of absolute risk estimates obtained with both conventional methods for survival analysis and competing-risk analysis.

The main difference between conventional methods for survival analysis and competing-risk analysis is the possibility to calculate the risk of more than one event when using the latter method. With competing-risk analysis researchers can calculate the risk of the main event, and the risk of one or several competing events. These competing events are defined by an event that either hinders or fundamentally alters the probability of having the main event [1]. For example, when studying a specific cause of death as the main event, death due to any other cause is a competing event, or when studying a specific primary treatment to a disease, any other primary treatment is a competing event.

An underlying assumption in conventional survival analysis is that censoring is non-informative, i.e. each study participant has the same probability of getting censored independent of their covariates. If the study participants' probability of getting censored depends on their covariates, the underlying assumption is violated (informative censoring). This could for instance happen when the studied risk factor is associated

with death (smoking, obesity, metabolic syndrome, etc.) or associated with any other competing event based on the study settings. To avoid violation of this assumption, an alternative is to include several events in the study by use of competing-risk analysis, and for example use overall death as a competing event to the main event of the study.

Example: Hypertension and Risk of Prostate Cancer

Here, we use data from the Metabolic Syndrome and Cancer project (Me-Can) [2], a prospective European cohort study of almost 290 000 men to illustrate the distinction between the study findings from conventional survival and competing-risk analyses. In Me-Can, we have previously studied metabolic factors and risk of prostate cancer using both methods [3,4].

This example focuses on the association between hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) and risk of prostate cancer. All men were followed from a baseline health examination (date of blood pressure assessment) until date of prostate cancer diagnosis, death, migration or end of follow-up, whichever occurred first. In this example we analysed data from 287 675 men, of whom 38% had hypertension at baseline health examination. Data of follow-up and results of performed regression analyses can be found in Table 1.

The absolute risk based on conventional survival methods using the Kaplan–Meier failure estimates is shown in Figure 1A. It shows that the risk of prostate cancer was similar for those with and without hypertension. Using competing-risk methods, we calculated the absolute risk of prostate cancer with the cumulative incidence function [5], as

shown in Figure 1B. Here, death was considered as a competing event to prostate cancer and we found that men with hypertension had a lower risk of prostate cancer compared with those without hypertension.

Despite providing different results, both estimates can be considered to be correct. Each figure aims to answer a different research question, which therefore often leads to misinterpretation. The risk as shown in Figure 1A can be interpreted as the risk of prostate cancer in a hypothetical scenario – men can only get prostate cancer and all other

events, including death, are censored. The risk in Figure 1B can be interpreted as the real-world risk, whereby men can get prostate cancer or die of any other cause. Other events (migration and end of follow up) are censored and assumed to happen at random regardless of hypertension status (or other covariates) at baseline.

There are two main reasons why our study findings differ when using these two methods. Firstly, prostate cancer is a disease of the elderly (mean age at diagnosis is about 70–72 years), and many men may have already died from other causes before they reach the age at which prostate cancer may be diagnosed. In a conventional survival analysis, this may result in an overestimation of the risk using Kaplan–Meier estimates [6]. In our example, this is reflected by the observed higher risk estimates of prostate cancer for both men with and without hypertension when using conventional methods (Fig. 1A), compared with competing-risk analysis (Fig. 1B). Secondly, there is an issue of informative censoring; hypertension is known to increase risk of death from all causes. More men with hypertension die and leave the study cohort, in comparison to men without hypertension. This could be a reason why there is no difference in the risk of prostate cancer between men with and without hypertension when using conventional analysis (Fig. 1A), compared with the competing-risk analysis (Fig. 1B).

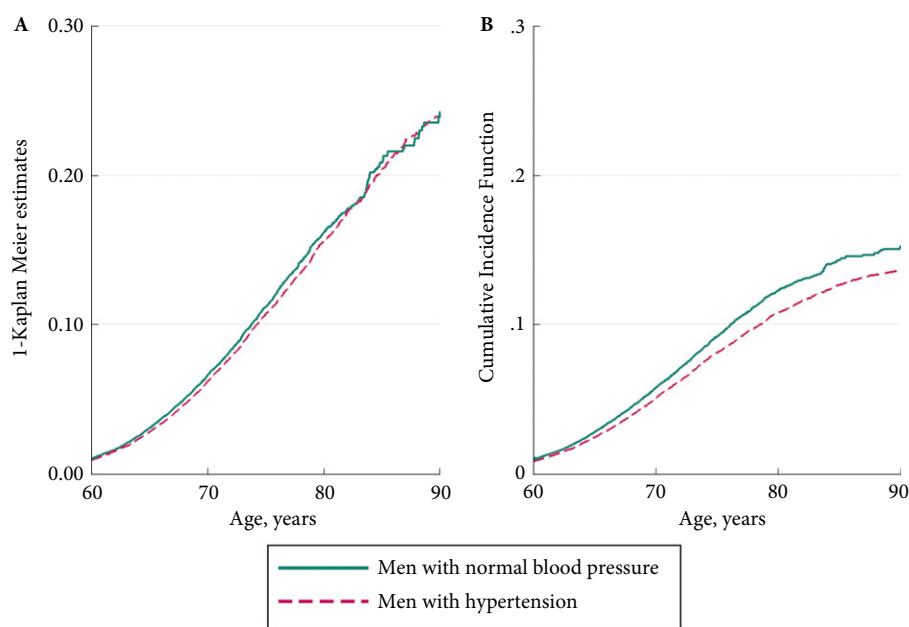
Despite correctly answering two different research questions, it is important to note that neither analysis gives any insight

Table 1 Results from follow-up and performed regression analyses.

	Men with normal blood pressure	Men with hypertension
Study subjects, <i>n</i> (%)	178 169 (62)	109 506 (38)
Number of prostate cancer cases, <i>n</i> (%)	3292 (2)	3615 (3)
Incidence rate of prostate cancer*	161.6	258.1
Number of deaths, <i>n</i> (%)	12 068 (7)	17 243 (16)
Incidence rate of death*	592.4	1231.1
Cox regression hazard ratio [†]	1.00 (Ref.)	0.99 (0.94–1.04)
Fine and Gray regression sub-distribution hazard ratio (95% CI) [‡]	1.00 (Ref.)	0.91 (0.87–0.96)

*Calculated per 100 000 men using conventional survival analysis censoring for all other events; [†]Adjusted for smoking (never, former, current), age at health examination (continuous) and stratified within the model for sub-cohort and date of birth (five categories); [‡]Adjusted for smoking (never, former, current), age at health examination (continuous), sub-cohort and date of birth (five categories).

Fig. 1 Absolute risk of prostate cancer among men with and without hypertension calculated by conventional survival analysis (**A**) and competing-risk analysis (**B**). The risk calculated by conventional methods reflects a hypothetical scenario in which men can only get prostate cancer and all other events are censored. The risk calculated by competing-risk analysis reflects the probability of a prostate cancer diagnosis in a real-world scenario, whereby death from other causes is taken into account.



in why men with hypertension have a lower risk of prostate cancer. Selection bias may explain these observations, but it is equally possible that men with hypertension have a different metabolic profile, which makes them less likely to develop prostate cancer. Thus, to the best of our knowledge, no statistical method can answer questions on aetiology like these in a scenario where competing risks are an issue.

To summarise, with this example we would like to encourage clinical researchers to distinguish between the risk calculated using conventional survival and competing-risk methods. In many study scenarios these two will result in similar findings, but in studies of populations with high mortality (e.g. elderly) or when the main exposure of interest is associated with a competing event (e.g. smoking or obesity and risk of death), the risk calculated from competing-risk analysis is required to provide a full understanding of the association studied.

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Conflicts of Interest

The authors declare that they have no competing interests.

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Abbreviations: Me-Can, metabolic syndrome and cancer project; mmHg, millimetre of mercury.